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10/731,672	12/09/2003	Shulamit Levenberg	0492611-0530/MIT-10077	6356

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EXAMINER	
SGAGIAS, MAGDALINE K	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
12/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/731,672	LEVENBERG ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50 and 59-74* is/are pending in the application.

4a) Of the above claim(s) *59-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50 and 71-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/9/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 7/18/08 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 59-74 are pending. Claims 6, 12, 20-21, 26, 35, 45-46, 51-58 are canceled. Claims 59-70 are withdrawn. Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 71-74 are under consideration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims **1-5, 7-11, 13-19, 22 remain** rejected under 35 U.S.C. 102(a) as being anticipated by **Levenberg et al,** (PNAS, 99(7): 4391-4396, 2002).

Levenberg teaches a tissue-engineering construct, comprising human embryonic stem cells, a three-dimensional cell support matrix, wherein cells are exposed to at least one growth factor in the endothelial growth medium EGM-2 which contains growth factors cytokines and supplements and wherein embryonic stem cells differentiate into three dimensional network formations of vascular network (abstract, p 4394, figure 3, p 4396, 2nd column under cell culture, p 4393). Levenberg teaches early endothelial progenitor cells isolated from differentiated mouse embryonic stem cells were shown to give rise to three blood vessel components, hematopoietic, endothelial and smooth muscle cells (p 4391, 1st column, 2nd paragraph).

Levenberg teaches the assembly of developing three dimensional vascular structure as soon as the cells acquired the set of endothelial markers (PECAM+) and the capillary area in the EBs increased during subsequent maturation steps up to day 13, starting from cell clusters that later sprout into capillary-like structures and eventually become organized in a network-like arrangement (p 4395, 2nd column, last paragraph). Levenberg teaches human ES cells, similar to mice ES cells, can spontaneously differentiate and organize *in vitro* in vessel-like structures in a pattern that resembles embryonic vascularization (p 4395, 2nd column, last paragraph). Levenberg teaches human ES cells induced to form EBs and spontaneously differentiate into the endothelial lineage, ultimately, forming three dimensional vascular structures and during EB differentiation some undifferentiated cells expressed high levels of Flk-1 inherently being smooth muscle cells and others became PCAM+ (endothelial cell marker) after EB formation and differentiation (p 4394, 2nd column, last paragraph) (**claims 1-3, 19, 22**).

Levenberg also teaches a tissue engineered construct wherein the cell support matrix comprises poly-(L-lactic acid) (PLLA) and poly lactic-glycolic acid (PLGA) mixed 1:1 (p 4392, 2nd column) (**claims 4-5, 7-11, 15**).

Levenberg also teaches the cell support matrix is biodegradable (p 4392, 2nd column) (**claims 14-15**).

Levenberg also teaches the cells were mixed 1:1 mix of culture medium and matrigel polymer sponges and the cell support matrix has a sponge shape (p 4392, 2nd column) (**claims 17-18, 22**).

Levenberg teaches the differentiation of human embryonic stem cells into endothelial cells forming vascular-like structures and smooth muscle cells (abstract and p 4393 and figure 2). **Levenberg** teaches the assembly of developing vascular-like structures could be observed during EBs outgrowth, as soon as the cells acquired the set of endothelial markers and smooth

muscle cells. The data also indicate that the capillary area in the EBs increased during subsequent maturation steps up to day 13, starting from cell clusters that later sprout into capillary-like structures and eventually become organized in a network-like arrangement (**claim 1**).

Further, the tissue engineered construct of **Levenberg** would inherently be resistant to contractile forces exerted by the stem cells and at least one growth factor selected to promote differentiation of the stem cells into smooth muscle cells. A product and its properties cannot be separated. The tissue engineered construct of Levenberg would inherently contain smooth muscle cells having the three a three dimensional vascular network as in the claimed method, since a three dimensional vascular network is composed of endothelial and smooth muscle cells around a lumen. As the three dimensional matrix of **Levenberg** cannot be distinguished from those claimed, the properties of the tissue engineering construct of **Levenberg** and those claimed would have the same properties.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971),

Northam Warren Corp. v. D. F. Newfield Co., 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01.

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art, does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Furthermore, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

Applicant is referred to MPEP 2112.

Thus, **Levenberg** et al, clearly anticipates the claimed invention.

Applicants argue that Levenberg does not anticipate Applicants presently pending claims because Levenberg does not teach or mention a tissue engineering construct comprising smooth muscle cells having a three dimensional vascular network as set forth in Applicants' claim 1. Rather, Levenberg speaks solely of endothelial cells and does not describe or teach one of ordinary skill in the art how to provide a tissue engineering construct comprising smooth muscle cells having a three dimensional vascular network. Absent a teaching of each and every element of Applicants' claim 1, Levenberg cannot anticipate claim 1 or claims 2-5, 7-11, 13-19, and 22 that depend therefrom. Accordingly, Applicants' submit that claims 1- 5, 7-11, 13-19, and 22 is novel in view of Levenberg.

These arguments are not persuasive because Levenberg clearly teaches Flk-1 positive cells which inherently are smooth muscle cells. Liebenberg's three dimensional construct is comprised of both endothelial cells and smooth muscle cells. Applicant's have not rebutted to the teachings of Levenberg would inherently be resistant to contractile forces exerted by the stem cells and at least one growth factor selected to promote differentiation of the stem cells into smooth muscle cells as cited in the previous office action and is maintained here. Levenberg clearly teaches a potential source of cells for engineered vessels are embryonic stem cells which, in murine systems, were shown to differentiate into endothelial cells that form vascular structures in a process called vasculogenesis and vasculogenesis is defined as the *in situ* assembly of capillaries from undifferentiated endothelial cells, and early endothelial progenitor cells isolated from differentiating mouse embryonic stem cells were shown to give rise to three blood vessel cell components, hematopoietic, endothelial, and smooth muscle cells and Levenberg cites reference (5) (p 4391, 1st column, 2nd paragraph). Reference (5), cited by Levenberg teaches Flk1+ cells derived from embryonic stem cells can differentiate into both endothelial and mural cells (pericytes and vascular smooth muscle cells) and can reproduce a vascular organization process. Reference (5) also teaches vascular endothelial growth factor promotes endothelial cell differentiation, whereas mural cells are induced by platelet-derived growth factor-BB. Vascular cells derived from Flk1+ cells can organize into vessel-like structures consisting of endothelial tubes supported by mural cells in three-dimensional culture. Thus, Levenberg teaches a tissue engineering construct comprising ES stem cells in a three dimensional cell support polymer matrix where platelet-derived growth factor-BB promotes differentiation of the stem cells into smooth muscle cells having a three dimensional vascular network as claimed in the instant invention. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims **1-5, 7-11, 13-19, 22, 23-,25, 27-34, 36-44, 47-50, remain** rejected under 35 U.S.C. 103(a) as being unpatentable over **Levenberg et al,** (PNAS, 99(7): 4391-4396, 2002) in view of **Benvenisty et al,** (US 2002/0146678).

Levenberg teaches a tissue-engineering construct, comprising human embryonic stem cells, a three-dimensional cell support matrix, wherein cells are exposed to at least one growth factor in the endothelial growth medium EGM-2 which contains growth factors cytokines and supplements and wherein embryonic stem cells differentiate into three dimensional network formations of vascular network (abstract, p 4394, figure 3, p 4396, 2nd column under cell culture, p 4393). Levenberg teaches early endothelial progenitor cells isolated from differentiated mouse embryonic stem cells were shown to give rise to three blood vessel components, hematopoietic, endothelial and smooth muscle cells (p 4391, 1st column, 2nd paragraph). Levenberg teaches the assembly of developing three dimensional vascular structure as soon as the cells acquired the set of endothelial markers (PECAM+) and the capillary area in the EBs increased during subsequent maturation steps up to day 13, starting from cell clusters that later sprout into capillary-like structures and eventually become organized in a network-like arrangement (p 4395, 2nd column, last paragraph). Levenberg teaches human ES cells, similar to mice ES cells, can spontaneously differentiate and organize *in vitro* in vessel-like structures in a pattern that resembles embryonic vascularization (p 4395, 2nd column, last paragraph).

Levenberg teaches human ES cells induced to form EBs and spontaneously differentiate into the endothelial lineage, ultimately, forming three dimensional vascular structures and during EB differentiation some undifferentiated cells expressed high levels of Flk-1 inherently being smooth muscle cells and others became PCAM+ (endothelial cell marker) after EB formation and differentiation (p 4394, 2nd column, last paragraph) (**claims 1-3, 19, 22**). **Levenberg** also teaches a tissue engineered construct wherein the cell support matrix comprises poly-(L-lactic acid) (PLLA) and poly lactic-glycolic acid (PLGA) mixed 1:1 (p 4392, 2nd column) (**claims 4-5, 7-11, 15**). **Levenberg** also teaches the cell support matrix is biodegradable (p 4392, 2nd column) (**claims 14-15**). **Levenberg** also teaches the cells were mixed 1:1 mix of culture medium and matrigel polymer sponges and the cell support matrix has a sponge shape (p 4392, 2nd column) (**claims 17-18, 22**). **Levenberg** teaches the differentiation of human embryonic stem cells into endothelial cells forming vascular-like structures and smooth muscle cells (abstract and p 4393 and figure 2). **Levenberg** teaches the assembly of developing vascular-like structures could be observed during EBs outgrowth, as soon as the cells acquired the set of endothelial markers and smooth muscle cells. The data also indicate that the capillary area in the EBs increased during subsequent maturation steps up to day 13, starting from cell clusters that later sprout into capillary-like structures and eventually become organized in a network-like **arrangement (claim 1).**

Further, the tissue engineered construct of **Levenberg** would inherently be resistant to contractile forces exerted by the stem cells and at least one growth factor selected to promote differentiation of the stem cells into smooth muscle cells. A product and its properties cannot be separated. The tissue engineered construct of Levenberg would inherently contain smooth muscle cells having the three a three dimensional vascular network as in the claimed method, since a three dimensional vascular network is composed of endothelial and smooth muscle cells

around a lumen. As the three dimensional matrix of **Levenberg** cannot be distinguished from those claimed, the properties of the tissue engineering construct of **Levenberg** and those claimed would have the same properties.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01.

"[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art, does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Furthermore, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373,

1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Applicant is referred to MPEP 2112. Levenberg does not teach the addition of retinoic acid thus, anticipating the growth factor is substantially free of retinoic acid. **Levenberg** differs from the claimed invention for not teaching exposing the embryonic stem cells to activin A.

However, at the time the claimed invention was made, **Benvenisty et al,** teach methods for mapping a pathway of differentiation of a population of embryonic stem cells which includes exposing the cells to Activin A and wherein cells differentiated into muscle-like syncytium (page 7, 2nd column, example 2). Benvenisty et al, reports while human embryonic stem cells have been recovered from human embryos produced by in vitro fertilization, the formation of embryoid bodies from human primates and from humans has been problematic and the formation of embryoid bodies from primates is inconsistent and asynchronous (p 1, 1st column). Benvenisty et al, have also suggested it is desirable to have tools to analyze and compare pathways indifferent mammals and to combine those these tools with a methodology that permits the isolation, preservation and cultivation of embryonic stem cells from mammals for transplantation in numerous human pathologies as a component in biomedical engineering (p 1 columns 1-2). As such, Benvenisty provides sufficient motivation for one of ordinary skill in the art to apply the three-dimensional cell support system of Levenberg exposing the cells to activin A wherein using human embryonic stem cells to analyze and compare pathways indifferent mammals and to combine those tools with a methodology that permits the isolation, preservation and cultivation of embryonic stem cells from mammals for transplantation in numerous human pathologies as a component in biomedical engineering.

Accordingly, in view of the teachings of Benvenisty et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the three dimensional construct of Levenberg by use human embryonic stem cells exposed to activin A

with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was taught by Benvenisty exposing embryonic stem cells to activin A, embryonic stem cells differentiate into muscle-like syncytium and particular as Benvenisty et al, have also suggested it is desirable to have tools to analyze and compare pathways in different mammals and to combine those these tools with a methodology that permits the isolation, preservation and cultivation of embryonic stem cells from mammals for transplantation in numerous human pathologies as a component in biomedical engineering.

Thus, the claimed invention as a whole is clearly prima facie obvious in the absence of evidence to the contrary.

Applicants argue that Levenberg and Benvenisty, either alone or in proper combination, do not render obvious Applicants presently pending claims because these references do not teach or fairly suggest a tissue engineering construct comprising smooth muscle cells having a three dimensional vascular network as set forth in Applicants' claim 1 or a method of making a tissue engineering construct comprising smooth muscle cells having a three dimensional vascular network as set forth in Applicants' claim 23. Applicants argue because Levenberg does not teach smooth muscle cells Benvenisty does not cure this deficiency in Levenberg and although Benvenisty does mention once in paragraph 0057 smooth-muscle cells this mention is the context of using cell cultures in place of animals for preclinical testing,

[0057] Additional uses for methods for providing cells that are differentiated partly or entirely along a particular cell lineage include in vitro uses such as creating reagents for drug toxicity assays. By adding drugs to cultures of differentiated cells such as kidney cells, liver cells, brain cells, heart smooth muscle, chondrocytes, pancreatic cells, neuronal cells, blood cells etc, it is possible to avoid the use of animals in preclinical testing...

this mention does not teach or suggest how one of ordinary art could provide one or more of Applicants' claimed inventions as a whole.

These arguments are not persuasive because Levenberg teaches smooth muscle cells for the reasons as discussed above and Bevensty provides for the same reasons as discussed above. Levenberg taken with Bevenisty provide teachings, suggestions and motivation to perform the instantly claimed method. The instant claims combine the elements of tissue engineering by using embryonic stem cells in a three-dimensional cell support polymer matrix and a growth factor to promote differentiation of stem cells into smooth muscle cells having three-dimensional vascular network, which taught by Levenberg taken with Bevenisty. This general method has been shown to be used successfully with growth factors, as expected and predictable function in the instantly claimed methods. Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. at, 82 USPQ2d at 1395. Therefore, in view of Levenberg taken with Bevenisty it would be prima facie obvious for one of skill in the art to add activin A to the construct of Levenberg to engineer a tissue construct to have tools to analyze and compare pathways in different mammals and to combine those these tools with a methodology that permits the isolation, preservation and cultivation of embryonic stem cells from mammals for transplantation in numerous human pathologies as a component in biomedical engineering.

It is noted that recent KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Ex Parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claims **71-74** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Levenberg et al,** (PNAS, 99(7): 4391-4396, 2002) in view of **Benvenisty et al,** (US 2002/0146678), and further in view of **Kojima et al,** (Experimental Cell Research, 206(2): 152-156, 1993).

The teachings of Levenberg taken with Benvenisty are applied here as indicated above. Levenberg taken with Benvenisty do not teach a tissue engineered construct with embryonic stem cells in serum-free medium and IGF.

However, at the time the invention was made, Kojima is an exemplified prior art that teaches that it is routine or well-established in the art to employ serum-deprived cells were incubated with activin A, nuclear labeling of bromodeoxyuridine occurred after a 12-h lag period. The effect of activin A on nuclear labeling was dose-dependent, being maximal at 10(-9) M. Activin A also increased the number of VSMC after 30 h of incubation. Insulin-like growth factor-1 (IGF-1) had only a small effect on nuclear labeling by itself but the effects of IGF-1 and activin A were additive. When quiescent VSMC were treated with activin A for 4 h, the effect of subsequent IGF-1 was markedly enhanced. Furthermore, activin A induced an autocrine production of IGF-1 in VSMC. In contrast to these positive effects on cell growth, activin A was rather inhibitory to the action of IGF-1 in activin-primed cells. In addition, activin A inhibited platelet-derived growth factor-induced nuclear labeling. These results indicate that activin A modifies growth of VSMC by complex mechanisms involving autocrine production of IGF-1 and modification of the action of IGF-1 (abstract).

Thus, it would also have been obvious for one of ordinary skill in the art of tissue engineering constructs for transplantation to further employ serum free conditions and IGF available in the art in tissue engineering of the combined cited reference. One of ordinary skill in the art would have been motivated to employ serum free and IGF conditions in order to

compare pathways indifferent mammals and to combine those these tools with a methodology that permits the isolation, preservation and cultivation of embryonic stem cells from mammals for transplantation in numerous human pathologies as a component in biomedical engineering when administered in vivo. One of ordinary skill in the art would have reasonably expected that further inclusions of serum free and IGF are routinely employed in the art and can help to further delineate VSMC by complex mechanisms involving autocrine production of IGF-1 and modification of the action of IGF, particularly in view of the totality of the prior art at the time the invention was made.

Thus, the claimed invention was prima facie obvious.

Applicants argue that for the same reasons as discussed above Levenberg and Benvenisty, either alone or in proper combination, fail to teach tissue engineering constructs comprising smooth muscle cells having a three dimensional vascular network and methods for making same as set forth in Applicants' claims. Applicants further submit that Kojima does not cure this deficiency in Levenberg and Benvenisty. Specifically, Kojima does not address a tissue engineering construct comprising embryonic stem cells and at least one growth factor selected to promote differentiation of the stem cells into smooth muscle cells having a three dimensional vascular network as set forth in Applicants' claim 1 or methods for producing a tissue engineering construct by, inter alia, exposing a population of embryonic stem cells to at least one agent selected to promote differentiation of the stem cells into smooth muscle cells having a three dimensional vascular network. Rather, Kojima is focused solely on the effects of chemical factors on mature, fully differentiated cells, and in particular on the nuclear labeling of such cells.

These arguments are not persuasive as discussed above regarding Levenberg and Benvenisty. With regard to Kojima again the this general method has been shown to be used successfully with growth factors, as expected and predictable function in the instantly claimed

methods. Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. at, 82 USPQ2d at 1395. Therefore, in view of Levenberg/Bevenisty taken with Kojima it would be prima facie obvious for one of skill in the art to add other growth factors to the construct of Levenberg/Bevenisty to further delineate VSMC by complex mechanisms involving autocrine production of IGF-1 and modification of the action of IGF, particularly in view of the totality of the prior art at the time the invention was made.

It is noted that recent KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Ex Parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pt. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396). Applicant's arguments focus on each reference individually. However, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The term "substantially free" in claim 72 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The concentration of retinoic acid is an all or none principle that is, it either exists or not exists. The rejection is maintained.

The term "substantially free" in claim 74 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The concentration of retinoic acid is an all or none principle that is, it either exists or not exists. The rejection is maintained.

It is noted Applicants have failed to respond to the above rejection, thus said rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter

Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

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